## Distal airway epithelial progenitor cells are radiosensitive to High-LET radiation.

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**Public Summary:**
Exposure to high energy radiation occurs in a variety of situations, including charged particle radiotherapy, radiological accidents, and space travel. However, the extent of normal tissue injury in the lungs following high energy radiation exposure is unknown. Here we show that exposure to high energy radiation led to a prolonged loss of in vitro colony forming ability by airway epithelial progenitor cells. Furthermore, exposure to high energy radiation induced clonal expansion of surviving progenitor cells in the distal airway epithelium. We discovered that the effects of high energy radiation exposure on progenitor cells occur in a p53-dependent manner. Our data show that high energy radiation depletes the distal airway progenitor pool by inducing cell death and loss of progenitor function, leading to clonal expansion of surviving progenitors. These findings have implications for radiation risk assessment and in understanding mechanisms of lung tissue remodeling following radiotherapy.

**Scientific Abstract:**
Exposure to high-linear energy transfer (LET) radiation occurs in a variety of situations, including charged particle radiotherapy, radiological accidents, and space travel. However, the extent of normal tissue injury in the lungs following high-LET radiation exposure is unknown. Here we show that exposure to high-LET radiation led to a prolonged loss of in vitro colony forming ability by airway epithelial progenitor cells. Furthermore, exposure to high-LET radiation induced clonal expansion of a subset of progenitor cells in the distal airway epithelium. Clonal expansion following high-LET radiation exposure was correlated with elevated progenitor cell apoptosis, persistent gamma-H2AX foci, and defects in mitotic progression of distal airway progenitors. We discovered that the effects of high-LET radiation exposure on progenitor cells occur in a p53-dependent manner. These data show that high-LET radiation depletes the distal airway progenitor pool by inducing cell death and loss of progenitor function, leading to clonal expansion. Importantly, high-LET radiation induces greater long-term damage to normal lung tissue than the relative equivalent dose of low-LET gamma-rays, which has implications in therapeutic development and risk assessment.